Development of a predictive model for the long term stability assessment of drug-in-adhesive transdermal films using polar pressure sensitive adhesives as carrier/matrix

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ABSTRACT

Drug crystallization in transdermal drug delivery systems (TDDS) is a critical quality defect. The impact of drug load and hydration on the physical stability of polar (acrylic) drug-in-adhesive (DIA) films was investigated with the objective to identify predictive formulation parameters with respect to drug solubility and long-term stability. Medicated acrylic films were prepared over a range of drug concentrations below and above saturation solubility; and were characterized by FTIR, differential scanning calorimetry (DSC), polarized microscopy and Dynamic Vapor Sorption (DVS) analysis. Physical stability of medicated films was monitored over four months under different storage conditions; and was dependent on solubility parameters, Gibbs free energy for drug phase transition from the amorphous to the crystalline state and relative humidity. DVS data, for assessing H-bonding capacity experimentally, was essential to predict physical stability at different humidities and was used together with Gibbs free energy change and the Hoffman equation to develop a new predictive thermodynamic model to estimate drug solubility and stability in DIA films taking into account relative humidity.

KEY WORDS

Polymeric drug delivery system, transdermal, crystallization, amorphous, physical stability, thermal analysis, hydration, water sorption, thermodynamics, mathematical model

ABBREVIATIONS AND SYMBOLS

a	activity
API	active pharmaceutical ingredient
ASA	acetylsalicylic acid
DIA	drug-in-adhesive
DSC	differential scanning calorimetry
DVS	dynamic vapor sorption
FTIR	Fourier transform infrared spectroscopy
GC	gas chromatography
HPLC	high performance liquid chromatography
IBU	ibuprofen
K	equilibrium constant
PSA	pressure sensitive adhesive
RH	Relative humidity
SAA	salicylic acid
T	Temperature
TDDS	transdermal drug delivery systems
*T*g	Glass transition temperature

x (or X) molar fraction

δ solubility parameter

ΔG_H Gibbs free energy of hydrogen bonding

ΔG_m Gibbs free energy of mixing

ΔG_v Change of Gibbs free energy upon crystallization

ΔH_f (or ΔH_{fus}) Enthalpy of fusion

ϕ volume fraction

χ Flory-Huggins interaction parameter

ω_i mass fraction of i

INTRODUCTION

Transdermal Drug Delivery Systems (TDDS), or transdermal patches, are dosage forms intended for delivering a drug across the skin into the systemic circulation. TDDS can have drug-specific benefits over conventional oral dosage forms as they by-pass the hepatic "first pass" metabolism and are devoid of gastro-intestinal side effects. They can also provide continuous drug delivery and stable plasma concentrations over an extended application time. Patches for passive drug delivery can be classified in four main types: drug-in-adhesive (DIA), drug reservoir membrane modulated systems, microreservoir systems as well as non-self-adhesive polymer matrices[1,2].

Drug release from passive diffusion-controlled TDDS depends on the chemical drug potential; however, stability issues can occur over time due to crystallization of the active pharmaceutical ingredient API[3]. Such change of the physical drug state is considered as a critical quality defect that may alter the adhesion-cohesion balance of the system, and more particularly drug release performance of the TDDS, thus leading to potential patient safety issues. Stable DIA acrylic films formulated with APIs possessing ideal physicochemical properties for passive skin diffusion are marketed already *e.g*. Nitro-Dur® or Minitran® containing nitroglycerin which has a melting point of 14°C and is present in liquid state at storage temperature. In contrast, APIs exhibiting a melting point above storage temperature *e.g.* estradiol (178°C), have a 'natural' tendency to recrystallize within the formulation if present above saturation solubility; as a consequence they are often formulated in matrix or reservoir patch designs using stabilisers in addition.

Three aromatic carboxylic acids; ibuprofen (IBU), salicylic acid (SAA) and acetylsalicylic acid (ASA) were formulated to DIA films using acrylic pressure sensitive adhesive (PSA). Acrylic PSA is polar, and may allow drug stabilization via H-bonding *inter alia*.

The aim of this work was therefore to define boundary conditions for drug crystallization inhibition in acrylic PSA using the Hoffman equation and assuming that Gibbs free energy change for the phase transition from the amorphous to the crystalline state (ΔG_v) is equal or higher compared to Gibbs free energy change of mixing i.e. the Gibbs free energy of H-bonding[4].

Different approaches for the prediction of drug crystallization in polymer matrix have already been described for solid dispersion applications only, based on thermodynamic[5–10], kinetic[11] or a combination of thermodynamic and kinetic principles[12]. Typical semi-empirical thermodynamic approaches consisted in using thermal analysis (recrystallization of supersaturated solid dispersions or melting point depression methods)[6–8], water sorption data[8,10] or solubility of API in low molecular weight analogue of polymer[7,8], to apply either Flory-Huggins or the regular solution theory, which however do not allow for hydrogen bonding interactions. Alternatively, Prudic et al.[9] applied a computational thermodynamic model (PC-SAFT) to solve the water vapor-

liquid and API solid-liquid equilibria to predict the impact of water sorption and API crystallization on API (indomethacin and naproxen) and polymer (PVP and poly(vinyl pyrrolidone-co-vinyl acetate)) solid dispersions. Mistry and Suryanarayanan[11] determined the crystallization times of solid dispersion using crystallization time of API and coupled relaxation times of saturated solid dispersions measured experimentally at different temperatures, but without evaluating the impact of humidity. Duarte et al.[12] used a computational method to estimate the microstructure of API-polymer systems, based on thermodynamic (Flory-Huggins theory), kinetic (Fick's second law of diffusion) and manufacturing (solvent evaporation) considerations to rank the polymers according to their miscibility with the drug (itraconazole). All the above models were developed for drug-hydrophilic polymer solid dispersions. There is currently no predictive model for the stability of drug-adhesive polymers, however due to the polar nature of the acrylic adhesive we could describe acrylic DIA films as drug-hydrophilic polymer solid dispersion systems.

Our approach takes into account the effect of drug load and relative humidity (derived experimentally by measuring DVS data) resulting in the development of a novel and simple predictive equation which considers both the effect of H-bonding and the effect of hydration on the physical stability of DIA films. This work is complementary to our paper describing the development of a predictive model for the estimation of stabilizer concentration in non-polar pressure sensitive adhesives[13].

MATERIALS AND METHODS

Materials

DuroTak 87-4287 was supplied by Henkel (Düsseldorf, Germany). SAA and ASA were acquired from Sigma-Aldrich (St Louis, MI, USA) and IBU from Knoll Pharmaceuticals (Nottingham, UK). HPLC grade ethyl acetate was purchased from Fisher Scientific (Fair Lawn, New Jersey, USA). Release liner Scotchpak 9755 and backing liner Scotchpak 9735 were supplied by 3M (St Paul, USA).

Methods

Estimation of solubility parameters

Solubility parameters δ of drugs and acrylic PSA were determined using Synthia software (Material Studio, Accelry's). This software allows the calculation of δ after input of the repeat

units of a polymer, thus, drug structures were each entered as monomer units by setting a tail atom and a head one. Acrylic adhesives are prepared from a mixture of different monomers (55-75% of 2-ethylhexyl acrylate, 2-6% of 2-hydroxyethylacrylate and 20-40% vinylacetate) but the exact composition is not disclosed by the manufacturer. Solubility parameter of acrylic adhesive was approximated by the solubility parameter of the main monomer, 2-ethylhexyl acrylate.

Calculation of drug solubility in adhesive

An estimate of equilibrium solute solubility was calculated, using the limiting form (2) of the Flory equation (1), for IBU, SAA and ASA[14,15]:

(1) $$\Delta G_m = RT\left[\underbrace{\ln\phi_1 + \left(1-\frac{\nu_1}{\nu_2}\right)(1-\phi_1)}_{Entropic} + \underbrace{\chi(1-\phi_1)^2}_{Enthalpic}\right]$$

Where ΔG_m is the Gibbs free energy of mixing of the drug and the polymer, χ is the Flory-Huggins interaction parameter between the drug and the polymer, $\phi_1$is the volume fraction of the drug (which can be approximated by the mass fraction of the drug), ν_1 and ν_2 are the molar volumes of the drug and the polymer respectively (in $cm^3.mol^{-1}$), T the temperature (298 K) and R the gas constant (8.314 J. $K^{-1}.mol^{-1}$).

Due to the important difference of molar volume of a small molecule (drug) compared to a polymer, it can be considered that $\frac{\nu_1}{\nu_2} \ll 1$ and $\phi_1 \ll 1$ (diluted solution). At equilibrium, $\Delta G_m = 0$

So, ϕ_1 at equilibrium can be approximated by:

(2) $$\phi_1 = \exp(-1+\chi)$$

With χ calculated using an extension of the Hildebrand-Scatchard theory of regular solutions[16]:

(3) $$\chi = 0.34 + \frac{\nu_1}{RT} \times (\delta_1 - \delta_2)^2$$

where δ_1 is the solubility parameter of the drug and δ_2 of the polymer (in $MPa^{1/2}$).

This equation is valid only in the case where there are no specific interactions between the drug and the polymer.

To evaluate the impact of physical dispersive forces on the free energy of the super-cooled drug liquid in the case of DIA systems, the regular solution equation[17] can be applied. For a mixture of drug and polymer, the activity coefficient of the drug can be estimated by using the solubility parameters of the PSA and the drug (δ_1 and δ_2, respectively) from the Scatchard-Hildebrand

equation (4)[17]. However, this theory has been developed for non-polar compounds, when the interactions are symmetrical and the molecules are distributed randomly:

(4)
$$ln(a_2/x_2) = \frac{v_2{\phi_1}^2}{RT} \times (\delta_1 - \delta_2)^2$$

Where a_2 is the drug activity, x_2 is the drug molar fraction, v_2 is the drug molar volume and ϕ_1 the polymer volume fraction and T the temperature (K). Assuming the heat capacity of the drug is constant, the drug activity can be approximated by:

(5)
$$lna_2 = -\frac{\Delta H_{fus}(T_m - T)}{RTT_m}$$

Where ΔH_{fus} is the enthalpy of fusion (J.mol^{-1}) of the drug and T_m its melting temperature (K). Then, the combination of (4) and (5) gives the regular solution equation:

(6)
$$ln(x_2) = -\frac{\Delta H_{fus}(T_m - T)}{RTT_m} - \frac{v_2{\phi_1}^2}{RT} \times (\delta_1 - \delta_2)^2$$

The drug mass fraction solubility in PSA can be estimated (from (6)) by assuming that the drug mass fraction solubility can be approximated by x_2 and that $\phi_1 \approx 1$.

Estimation of the driving force for drug recrystallization (Hoffman equation)

The prediction of drug solubility at equilibrium in acrylic adhesive was calculated based on the driving force for drug recrystallization from the Hoffman equation[18], i.e. the chemical energy gained by the phase transition from the amorphous to the crystalline state:

(7)
$$\Delta G_v \approx -\frac{\Delta H_{fus}(T_m - T)T}{T_m^2}$$

Where ΔG_v is the change in Gibbs free energy upon crystallization (J.mol^{-1}), ΔH_{fus} the enthalpy of fusion (J.mol^{-1}), T_m the melting temperature (K) and T the temperature (K).

2.2.4 Determination of solid content of liquid adhesives

The solid content of liquid adhesive was measured gravimetrically according to Wolff et al[15]. Results were verified by examination of residual solvent using Headspace Gas Chromatography as described in the following section. The mean value of solid content was subsequently used for the calculation of the required amount of liquid adhesive for each target drug load in medicated films.

Residual solvent analysis

Residual solvent in dry adhesive and drug-in-adhesive (DIA) films was determined by Headspace Gas Chromatography (GC) (Agilent Technologies 7890A, Santa Clara, CA, USA). Ethyl acetate is a class 3 solvent and its overall concentration in pharmaceutical products should be less than 5000 ppm (or 0.5% (w/w))[19].

Calibration curves were prepared using five solutions of ethanol and ethyl acetate in internal standard (toluene) for the quantification of solvent residues in dry adhesive and DIA films.

20cm^2 of dried three-layer system samples (backing membrane/adhesive layer/release liner) (n = 3) were punched and the release liner was removed. The remaining film was introduced into a 20ml headspace vial containing 5ml of internal standard and the vial was capped immediately. A blank of internal standard was injected at the start of each run.

A DB-624 (30 x 0.53mm x 3.0µm) GC column was used with helium gas as the carrier (constant flow of 35cm/min) with 3.5 psi gas pressure. The United State Pharmacopoeial method, USP 467, for the Headspace analysis of organic volatile impurities was applied[20].

Total solvent residues were less than 0.2 % (w/w) in every sample.

Coating and drying of DIA films

The release liner (3M Scotchpak 9755) was cut to the required length to fit the Erichsen Model 509/1 film coater (Hemer-Sundwig, Germany) with the release coating side facing up. The solutions were coated onto the release liner sheet. The knife blade was set to a height of 250 µm and the speed of the blade was set to 6 mm/s. The coated solutions were then dried using a universal oven (Memmert Model UNE 400, Schwachbach, Germany) at controlled temperature and the dried films were laminated with a 3M Scotchpak 9735 backing liner. Drying conditions were adjusted so that residual solvents did not exceed 0.2% (w/w). Optimized drying conditions were found to be 15 min at 50°C.

Preparation of DIA-type films

DIA-type films were prepared at different drug concentrations (detailed in Table 1), in order to get an estimate of the drug saturation solubility in the dry adhesive.

An accurately weighed mass of drug was introduced in a tared container. An accurate mass of liquid adhesive was then added in the same container, which was quickly capped to minimize solvent evaporation and the mixture was stirred at about 150 rpm overnight, using an overhead stirrer (IKA, Staufen, Germany).

The solution was then coated and dried as described previously and three films were prepared per solution. Three 20 cm^2-samples were subsequently punched per film and analyzed using headspace gas chromatography to verify that solvent residues did not exceed 0.2%w/w. The mean coating weight (n = 3 or 4) and film thickness (n = 5) were measured per film (intra-film mean) and then averaged (inter-film mean, n = 3).

Table 1. Compositions of DIA films (dried for 15 min at 50°C). Mean film thicknesses ranged from 95 to 105 µm (film coating weights from 7.3 to 8.5 $mg.cm^{-2}$).

Differential Scanning Calorimetry (DSC)

Examination of the thermal behavior of pure drugs and adhesive films was carried out with a DSC Q1000 (TA Instrument, USA) purged with dry nitrogen (50 ml/min). Calibration of the instrument was established using indium standard.

Samples were accurately weighed using a microbalance (Mettler MT5, Mettler-Toledo, Greifensee, Switzerland) and introduced into aluminum hermetic pans and lids. Standard heat/cool/heat cycles (heating and cooling rate of 5°C/min or 10°C/min) were performed in triplicate (see Table 2), with cycle 1 corresponding to the first heat, cycle 2 the cooling and cycle 3, the second heat. Melting points and enthalpies of fusion were recorded from the melting endotherms of the first heat, whereas glass transition temperatures (Tg) were recorded from the second heat.

Table 2. DSC tests temperatures.

Polarized Microscopy

Medicated films were observed under a microscope (Olympus BH-2, Olympus Corporation, Tokyo, Japan) fitted with a 10× magnification lens, a camera (AxioCam, MRc, Carl Zeiss, UK) and AxioVision vs4.4 software. Polarized light was used in order to determine whether the

particles observed were crystalline. The scale of the microscope was calibrated for each magnification using graticules of 1mm.

Dynamic Vapor Sorption (DVS)

Dynamic vapor sorption experiments were performed on pure compounds and drug-in-acrylic films, using a DVS Advantage 1 instrument (Surface Measurement Systems UK Ltd., London, UK) equipped with a recording ultra-microbalance exhibiting a mass resolution of 0.1μg. A quantity of sample of typically 8 to 12mg was placed into a tared aluminium pan, which was placed on the DVS pan. The temperature was maintained constant at 25 ± 0.1°C and the sample was exposed to 0.00 partial pressure (in order to record its dry mass) and then to the following water vapor partial pressure profiles: 0.20, 0.40, 0.60, 0.80 and 0.90 p/p0. The partial pressure was then decreased in an identical manner to 0.00 p/p0. Each step lasted until the mass variation over time of the sample was lower than 0.002%.min^{-1}, so that the sample mass reached equilibrium. The sorption isotherms were calculated from the equilibrium mass values at each partial pressure, using the change in mass with respect to the dry mass.

Exploratory stability studies

Samples of 20cm^2 each (n = 3) were punched from fresh binary mixture layers and DIA films. Each one was stored at a different condition:

- at 25.0 ± 0.6°C and at 70 ± 1 % RH into a monitored oven **(c_1)**,
- at ambient temperature (21 ± 2°C) and at low RH (0.9 ± 0.7%) into a cabinet (in the presence of phosphorus pentoxide) **(c_2)**,
- at ambient (21 ± 2°C) temperature and ambient RH (37 ± 7%) **(c_3)**.

Samples were observed at regular intervals using polarized microscopy to detect any crystallization. DSC analyses were also performed to confirm the microscopy results.

Statistical analysis

T-tests and one way analysis of variance (ANOVA) were used to analyze DVS data using SPSS version 18 (SPSS UK Ltd, IBM, Woking, UK). Post hoc analysis was carried out with the Scheffe method and a level of significance of 95% (p = 0.05). When criteria of normality and homogeneity were not met, non-parametric tests were performed (Mann-Whitney).

RESULTS AND DISCUSSION

Exploratory stability studies

Results of the stability studies (Table 3) carried on drug-in-acrylic adhesive films allowed experimental approximation of drug solubility in dry acrylic (Table 4). Thermal properties of pure drugs and DIA films were also determined using DSC (Table 5). The *T*g values of the DIA films were lower than the *T*g values of the pure acrylic, indicative of the plasticizing effect of the drug.

Table 3. Physical stability of drug-in-acrylic films at different storage conditions

IBU-in-acrylic films at 20%(w/w) exhibited edge effect depending on storage conditions (edge effect was more prevalent at high storage humidity). Instability was confirmed by DSC, which showed, after storage, a melting endotherm corresponding to crystalline ibuprofen. The acrylic film containing 17%(w/w) of IBU remained clear and stable. Thus saturation solubility of IBU in acrylic adhesive was between 17% and 20%(w/w).

SAA films remained crystal-free at 7%(w/w) but not at 13.5%(w/w) loading. ASA films were stable at drug load of 4%(w/w) but exhibited crystallization at 7%(w/w), consistent with DSC results. Hence, solubility of SAA in acrylic films was between 7% and 13.5%(w/w) and solubility of ASA in acrylic films was between 4% and 7%(w/w).

Solubility parameter of acrylic adhesive was determined using the solubility parameters of 2-ethylhexylacrylate to be 19 $MPa^{1/2}$. The prediction of drug solubility in acrylic adhesive estimated using the previously disclosed Flory-Huggins equation (Equation 2) gave results in partial agreement with experimental observations (Table 4); i.e. a good fit was observed for IBU and ASA whereas solubility calculations for SAA were not in agreement with experimental data.

Table 4. Comparison of theoretical and experimental drug solubility in acrylic PSA at 25 °C.

Table 5. Thermal properties of pure compounds, unsaturated and saturated fresh DIA films (determined experimentally)

The observed deviations in the case of SAA may be explained by the fact that SAA formed strong dimers, which impacted its solubility parameter[22]. The solubility parameter of SAA dimer was actually lower, 22.1 $MPa^{1/2}$ [23,24], as the dimer was less available for hydrogen bonding, leading to a smaller difference in solubility parameters between drug and PSA and thus higher predicted saturation solubility. As neither of the calculated solubilities of monomeric and dimeric SAA using the Flory-Huggins equation were in agreement with the experimental results, it could be postulated that there was a mixture of monomer and dimer SAA in the DIA systems.

In addition, the regular solution theory was valid for non-polar compounds and the mass fraction solubility was actually approximated by the molar fraction leading to an uncertainty on solubility parameter calculation. Prediction of drug solubility in pure adhesives was done using the limiting form of Flory-Huggins equation (and the regular solution equation) assuming that they did not interact specifically (*e.g.* acid-base reaction or defined complex formation) with the drugs[25]. Acrylic adhesive holds polar moieties and therefore, an alternative approach was developed, taking into account dipole-dipole or hydrogen bonding interactions between the drugs and acrylic adhesive.

Predictive model development and implementation

The entropic term and physical forces terms accounting for non-hydrogen bonding solubility parameters could be neglected in the modified Flory-Huggins equation[14,26] in the investigated formulations:

$$\frac{\Delta G_m}{RT} = \overbrace{\left[\frac{\phi_1}{M_1}\ln\phi_1 + \frac{\phi_2}{M_2}\ln\phi_2\right]}^{entropic\ term} + \overbrace{\phi_1\phi_2\chi}^{physical\ forces\ term\ (non\ H-bonding)} + \overbrace{\frac{\Delta G_H}{RT}}^{H-bonding} \quad \textit{(8)}$$

ΔG_m is the Gibbs free energy of mixing of the drug and the polymer, χ is the interaction parameter between the drug and the polymer, ϕ_1 is the volume fraction of the drug (which may be approximated by the mass fraction of the drug) and ϕ_2 of the polymer, M_1 and M_2 the molecular weights of the drug and the polymer respectively, T the temperature (298 K), R the gas constant (8.314 J. K^{-1}.mol^{-1}) and ΔG_H the Gibbs free energy of hydrogen bonding between the drug and the polymer (generally favourable to mixing). This term ΔG_H does not take into account the physical interaction contribution (included in second term). The first term is for the changes of entropy (entropy of disorientation and localization) upon mixing. The second term is an enthalpic term related to non-hydrogen-bonding interactions between the polymer and the solute, which are

defined by the usual interaction parameter χ. The derivation of (8) does not involve more assumptions than the usual Flory-Huggins equation and polymer lattice theory and includes the changes in entropy and enthalpy of hydrogen bond formation upon mixing of a polymer and a solute that interact via H-bonding.

DVS data of pure APIs and unsaturated drug-in-acrylic films are shown in Figure 2a and b, respectively. Fig 2b shows that pure acrylic films absorbed less moisture than drug loaded films (p = 0.025). Considering that water uptake by pure APIs was negligible, the increase in water uptake by the drug loaded acrylic films could be due to the different microstructure between unmedicated and medicated acrylic films; incorporation of drug molecules resulted in 'breakage' of intra-molecular hydrogen bonds between polymer chains of the adhesive, as a result of drug/acrylic polymer H-bonding interaction, leading to an increase in the number of sites (of polymer) available for binding with water. As such, the medicated film microstructure consisted of additional polar groups from the acrylic polymer, compared to the unmedicated film, available for water absorption. During the DVS measurements, H_2O is replacing drug molecules bound via hydrogen bonding to the polymer and therefore the DVS data is an indicator for drug-polymer interaction via H-bonding. This replacement of drug molecules by water molecules also explains the "hydration effect" in DIA films, which enables drug release upon skin application. Drug/acrylic H-bonding can retain the stability of the DIA film during storage; when the film is applied to the skin, moisture uptake from the stratum corneum breaks the drug/polymer H-bonds enabling the free unbound drug molecules to diffuse into the stratum corneum. However this phenomenon also reiterates the need for appropriate packaging and storage of the DIA films at low humidity conditions, in order to retain the physical stability of the film.

Water sorption of saturated drug-in-acrylic films was higher compared to their respective unsaturated drug-in-acrylic film especially for SAA and ASA (p = 0.016), (Figure 2b(i) and b(ii)). This difference in water sorption between saturated and unsaturated DIA films correlates well and can be explained by the different Tg values of these films (Table 5); saturated films had lower Tg value compared to their unsaturated counterpart, indicating that an increase in drug concentration in the film had a more prominent plasticizing effect, leading to increased molecular mobility in the film and increased water sorption. Whereas the similar Tg value for saturated (20%(w/w)) and unsaturated (17%(w/w)) ibuprofen-in-acrylic films correlated with their similar water sorption, indicating that the 17%(w/w) film was already saturated.

All unsaturated drug-loaded acrylic films showed similar water uptake values, independent of drug type, whereas saturated films showed variable water uptake (Figures 2b(i) and b(ii)). This latter variability can be correlated with the Tg data and thus can be attributed to variability in the

plasticizing effect and also to variability in intramolecular H-bonding among drug molecules; for example stronger H-bonding interaction between SAA molecules increased the availability of acrylic polar groups for water binding and combined with an increased plasticizing effect, resulted in higher water sorption compared to saturated films containing IBU or ASA.

The drug portion which was subject to H-bonding with the functional groups of the acrylic adhesive was in equilibrium with the portion of free dissolved (non-interacting, non-amorphous) drug.

The new predictive model is based on Gibbs free energy change for H-bonding (ΔG_H), which can be expressed by:

(9) $$-\Delta G_H = -RT \ln K$$

With

(10) $$K = \frac{X_F}{X_B} = \frac{\omega_F}{\omega_B}$$

Where X_F and X_B are the mole fractions of free drug and bound drug, respectively and ω_F and ω_B the mass fractions, *i.e.* $X_F + X_B = 1$ (or $X_F = 1 - X_B$).

Consequently,

(11) $$X_F = \frac{K}{1+K}$$

Also, it can be approximated that

(12) $$\Delta G_H \approx \Delta G_m$$

To get a stable semi-solid drug solution, Gibbs free energy change for the phase transition from the amorphous to the crystalline state (ΔG_v) has to be equal or higher (actual values) compared to Gibbs free energy change of mixing (or Gibbs free energy of H-bonding). Consequently, at equilibrium:

(13) $$\Delta G_v \approx \Delta G_H$$

And by combining (9) and (12)

(14) $$K \approx \exp\left(\frac{\Delta G_v}{RT}\right)$$

By combining (11) and (14), it can be deduced that:

(15)

$$X_F = \frac{\exp\left(\frac{\Delta G_v}{RT}\right)}{1 + \exp\left(\frac{\Delta G_v}{RT}\right)}$$

This means that, for a drug/acrylic polymer mixture the fraction 1-X_F needs to be stabilised by hydrogen bonding. A fraction of 1-X_F of binding sites is therefore required. In other words, X_F (or ω_F) represents the maximum fraction of free drug that is allowed to get a stable system characterized by a reduced chemical potential of the drug due to drug-polymer interactions via hydrogen bonding. Accordingly, X_F (or ω_F) can be taken as an estimate for drug solubility in tested systems provided that number of interacting functional groups is sufficient for hydrogen bonding interactions.

A modified correction factor for estimating the impact of water on the formulation was introduced, as hydrogen bonding depends on the number of polymer segments available for drugs with hydrophilic functional groups. This number f_{acr} decreases with hydration (increase of RH) and was calculated according to equation (16). The mole number of water (n_{H_2O} in mol/100g of sample) was calculated from water sorption isotherms results of drug-loaded adhesive films:

(16)

$$f_{acr}(RH) = \frac{n_{drug}}{n_{drug} + n_{H_2O}}$$

Where n_{drug} is the total molar quantity of drug, in mol/100g of sample.

By multiplying this factor with the calculated free drug molar fraction, estimation for stable unbound drug concentrations, the mass fraction solubility, at different relative humidity (RH) values is possible:

(17)

$$\omega_{s\,(corr)}(RH) = \omega_F \times f_{acr} \times 100$$

The correction factors f_{acr} are listed in Table 6. Table 7 shows the predicted drug solubility in acrylic adhesive after correction, in comparison to experimental data. According to Table 7, the solubility of the tested carboxylic acids is decreasing with increasing relative humidity. The ratio between the tested drug concentration and the saturation solubility is shown in Figure 4. Values greater than 1 direct to an unstable or metastable physical state. The predicted solubility was in good agreement with physical stability observed for high and reduced drug loads.

Table 6. Correction factors f_{acr} for drug-in-acrylic films (drug loading % (w/w) shown next to each drug) obtained from water sorption data at (25°C).

Table 7. Predicted drug solubility at different relative humidities (RH) (in % (w/w)) at 25 °C.

Experimental data and predicted drug solubility in acrylic adhesive were compared (Table 8): Tested higher drug loads were not physically stable, in agreement with the prediction, due to the reduction of solubility caused by the hydration effect. To investigate in more detail the impact of water absorption on drug solubility, DVS studies and long-term physical stability tests were performed on samples with lower drug loads. As predicted, samples of low drug loads were shown to be stable under test conditions (up to 70% RH). In conclusion, this is a reliable mathematical approach which enables the prediction of a stable drug load and long-term stability of drug-in-acrylic films.

Table 8. Stability of acrylic-type test samples manufactured with Duro-Tak 87-4287 compared to predicted solubility

There was a good agreement between experimental and calculated results using the DVS data. Besides, the predicted solubility values using water sorption data (equation (17)) were closer to experimental results than predicted solubilities using the limiting form of Flory-Huggins equation, especially in the case of SAA (due to the imprecision on the different solubility parameters of the monomer and dimer forms of the drug). The Flory-Huggins equation allowed the prediction of drug solubility based on solubility parameters and appropriate estimate of the interaction parameter χ. However it does not take into account the impact of polymorphism, contrary to regular solution equation and the estimation of drug solubility using the above approach which is based on hydrogen interactions and the Hoffman equation with respect to DVS data. Using this latter approach, the free energy change for crystallization was compared with the Gibbs free energy of mixing. The observed impact of hydration on saturation solubility confirmed that Gibbs free energy of hydrogen bonding largely governed the change of Gibbs free energy of mixing in the tested acrylic adhesive. Flory-Huggins theory has also been used for ternary mixtures of API-polymer-water to determine the impact of RH on miscibility[8,10], which only allowed a qualitative evaluation. Moreover, application of this equation from data generated by the melting point depression method led to imprecise results (low correlation coefficient[8]) which were dependent on experimental heating rate as shown by Knopp et al.[5]. Rask et al.[7] also emphasized that solubility measurements using recrystallization of supersaturated amorphous dispersions should be considered with caution.

A different approach was employed for solid dispersions intended for oral formulation by Prudic et al.[9], which involved modelling and thermal analysis. The authors used a thermodynamic model, Perturbed Chain-Statistical Association Fluid Theory, which determined the residual Helmholtz energy by describing a molecule as a chain of segments and experimental data on binary systems to solve simultaneously vapor-liquid equilibrium of water (moisture) and liquid-solid equilibrium of API (amorphous/crystalline). Similarly to our model, it considered hydrogen bonding interactions and the impact of relative humidity, but required a more complicated implementation as opposed to our approach.

CONCLUSION

For the tested DIA acrylic systems, experimental results were compared to the solubility calculated using the limited form of Flory-Huggins equation, as well as using the regular solution equation which considers both the heat of fusion and the solubility parameter difference. Assuming that the drug was able to interact via hydrogen bonding with the acrylic adhesive, a thermodynamic approach was developed for DIA systems based on the Hoffman equation to estimate the drug saturation solubility and stability from DSC and DVS data, hence avoiding the use of solubility parameters. Water sorption studies on pure drugs, pure acrylic PSA and on acrylic DIA showed that acrylic DIA samples absorbed a greater amount of water than the pure acrylic PSA. The resulting calculated drug solubility in acrylics appeared to be in a good agreement with the experimental stability results.

$$\omega_{s\,(corr)}(RH) = \omega_F \times \frac{n_{drug}}{n_{drug} + n_{H_2O}} \times 100$$

ACKNOWLEDGMENTS

We are grateful to UCB Biosciences for the financial support of this PhD work. We would like to thank Henkel for the supply of DuroTak 87-4287 samples and 3M for the supply of release and backing liner samples.

DECLARATION OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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FIGURE LEGENDS

Figure 1. Chemical structure of selected drugs and acrylic PSA (polyacrylate).

Figure 2. a) Water sorption isotherms of pure drugs (*n*=3); **b)** Water sorption isotherms of **(i)** unsaturated, and **(ii)** saturated drug-in-acrylic films in comparison to the pure adhesive (*n*=3)

Figure 3. Different states of the drug in the acrylic matrix.

Figure 4. Plot of the ratio between tested concentration and calculated solubility (depending on relative humidity, at 25°C). Values lower than 1 indicate unsaturation, greater than 1 saturation.

LEGEND FOR THE GRAPHICAL ABSTRACT

Drug solubility in the acrylic matrix.